Neurosurg Rev (2016) 39:241–249
DOI 10.1007/s10143-015-0682-7

ORIGINAL ARTICLE

# Difference of language cortex reorganization between cerebral arteriovenous malformations, cavernous malformations, and gliomas: a functional MRI study

Xiaofeng Deng[1,2,3,4] · Long Xu[1,2,3,4] · Yan Zhang[1,2,3,4] · Bo Wang[5] · Shuo Wang[1,2,3,4] · Yuanli Zhao[1,2,3,4] · Yong Cao[1,2,3,4] · Dong Zhang[1,2,3,4] · Rong Wang[1,2,3,4] · Xun Ye[1,2,3,4] · Jun Wu[1,2,3,4] · Jizong Zhao[1,2,3,4]

Received: 24 January 2015 / Revised: 5 July 2015 / Accepted: 9 August 2015 / Published online: 13 November 2015




**Abstract** The authors attempted to demonstrate the difference in language cortex reorganization between cerebral malformations (AVMs), cavernous malformations (CMs), and gliomas by blood oxygen level-dependent (BOLD) functional magnetic resonance imaging. Clinical and imaging data of 27 AVM patients (AVM-L group), 29 CM patients (CM-L group), and 20 glioma patients (Glioma-L group) were retrospectively reviewed, with lesions overlying the left inferior frontal gyrus (Broca area). As a control, patients with lesions involving the right inferior frontal gyrus were also enrolled, including 14 AVM patients (AVM-R group), 20 CM patients (CM-R group), and 14 glioma patients (Glioma-R group). All patients were right-handed. Lateralization indices (LI) of BOLD signal activations were calculated separately for Broca and Wernicke areas. In AVM-L group, right-sided lateralization of BOLD signals was observed in 10 patients (37.0 %), including 6 in the Broca area alone, 1 in the Wernicke area alone, and 3 in both areas. Three patients (10.3 %) of CM-L group showed right-sided lateralization in both Broca and Wernicke areas, and 1 patient (5.0 %) of Glioma-L group had right-sided lateralization in the Wernicke area alone. A significant difference of right-sided lateralization was observed between the AVM-L group and CM-L group ($P$=0.018) and also between the AVM-L group and Glioma-L group ($P$=0.027). No patient in AVM-R, CM-R, or Glioma-R groups showed right-sided lateralization. Language cortex reorganization may occur in AVM, CM, and glioma patients when the traditional language cortex was involved by lesions,

Xiaofeng Deng and Long Xu contributed equally to this work.

✉ Jizong Zhao
zhaojz205@163.com

Xiaofeng Deng
windmessenger@126.com

Long Xu
forrest1204@139.com

Yan Zhang
YanZhang135@163.com

Bo Wang
bwang@bcslab.ibp.ac.cn

Shuo Wang
captain9858@vip.sina.com

Yuanli Zhao
zhaoyuanli@126.com

Yong Cao
caoyong6@hotmail.com

Dong Zhang
zhangdong0660@aliyun.com

Rong Wang
Ronger090614@126.com

Xun Ye
yexun79@hotmail.com

Jun Wu
wujunslf@126.com

1 Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China

2 China National Clinical Research Center for Neurological Diseases (NCRC-ND), Beijing, China

3 Center of Stroke, Beijing Institute for Brain Disorders, Beijing, China

4 Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, Beijing, China

5 State Key Laboratory of Brain and Cognitive Science, Beijing MRI Center for Brain Research, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China

but the potential of reorganization for CM and glioma patients seems to be insufficient compared with AVM patients.

**Keywords** Language cortex reorganization · Arteriovenous malformation · Cavernous malformation · Glioma · Functional MRI · Aphasia

## Introduction

Arteriovenous malformations (AVMs) and cavernous malformations (CMs) are common pathologies among cerebral vascular diseases, which are both generally considered as congenital lesions. However, AVMs are pathologically characterized by direct communication of arteries to abnormal veins without interposing capillaries and it may include brain parenchyma within the nidus [1, 2], whereas CMs are composed of thin hyalinized vascular channels without interposed brain tissue [3, 4].

Clinically, although AVMs may grow in eloquent areas such as language cortex, they usually do not lead to neurological function deficits unless ruptured. It is postulated that when they develop in the usual anatomical sites of language cortex, cortical reorganization will result in language areas displaced to other regions, either to the homologous regions on the contralateral hemisphere or to the cortex surrounding the lesion on the same hemisphere. Language function will therefore remain intact [5].

However, compared with AVMs, the report of language reorganization in CMs is really rare. It is hypothesized that the CM lesions might be too small to induce reorganization [6]. The language reorganization for CM patients is seldom evaluated, and little is known about the difference of language cortex reorganization between AVM and CM patients.

Meanwhile, gliomas are thought to be acquired diseases and the duration of illness is relatively short. Aphasia is a common presentation for patients with gliomas involving language areas, and right-sided language dominance in right-handed patients is seldom reported [7–9].

In this study, we applied blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) to study the BOLD signal activations, in order to evaluate language dominance in AVMs, CMs, and gliomas. Considering activation in both hemispheres is a common phenomenon in fMRI images, the lateralization index (LI) was used to quantify the degree of lateralization of BOLD signal activations, and LIs of the Broca and Wernicke areas were separately studied, as well as the global LI. Difference of language lateralization between these three lesions was systemically evaluated.

## Materials and methods

After the study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University, we retrospectively reviewed the medical records and imaging studies of 27 AVM patients (AVM-L group), 29 CM patients (CM-L group), and 20 glioma patients (Glioma-L group), with all lesions located in or near the Broca area (left inferior and middle frontal gyri, including Brodmann area 44, 45, 9, 46). As a control, patients with lesions involving the right inferior frontal gyrus were also enrolled, including 14 AVM patients (AVM-R group), 20 CM patients (CM-R group), and 14 glioma patients (Glioma-R group). All patients were right-handed native Chinese (Mandarin) speakers from mainland China and underwent preoperative fMRI between the years 2006 and 2014.

Patients with a history of lesion rupture and hemorrhage within 3 months were excluded from this study. Besides, to make the lesion volume less variable, lesions with the maximum diameter larger than 40 mm were also excluded.

### Patient population

AVM-L group enrolled 12 male and 15 female patients, with ages ranging from 10 to 52 years (mean±SD 28.1± 12.1 years). Main clinical presentations included seizures in 20 patients, headache in 5, aphasia in 1, and weakness of limbs in 1.

AVM-R group included 9 males and 5 females, and the mean age was 27.7±10.9 years (range 12 to 46 years). Twelve patients presented with seizures, 1 with headache, and 1 with weakness of limbs.

In CM-L group, there were 14 male and 15 female patients, with ages ranging from 13 to 64 years (mean±SD 32.3± 12.4 years). Main symptoms included seizures in 13 patients, weakness of limbs in 4, headache in 4, paresthesia in 3, aphasia in 3, and asymptomatic in 2 patients.

CM-R group enrolled 11 males and 9 females, with ages ranging from 10 to 60 years (mean±SD 32.2±12.0 years). Eleven patients presented with seizures, 2 with weakness of limbs, 2 with headache, and 2 with paresthesia, and 3 patients were asymptomatic.

In Glioma-L group, there were 11 males and 9 females, with ages ranging from 20 to 64 years (mean±SD 42.2± 14.3 years). Main symptoms included aphasia in 9 patients, weakness of limbs in 4, headache in 3, paresthesia in 2, and seizures in 2 patients. Duration of symptoms ranged from 1 to 32 months (mean±SD 7±3 months). According to the World Health Organization (WHO) brain tumor grading system (2007) [10], 6 patients were pathologically diagnosed with diffuse astrocytoma (WHO grade II), 3 with oligodendroglioma (WHO grade II), 4 with oligoastrocytoma

(WHO grade II), 1 with anaplastic oligoastrocytoma (WHO grade III), and 6 with glioblastoma (WHO grade IV).

In Glioma-R group, there were 7 males and 7 females, with ages ranging from 23 to 62 years (mean±SD 40.8±12.8 years). Main symptoms included seizures in 8 patients, weakness of limbs in 2, headache in 2, and paresthesia in 2 patients. Duration of symptoms ranged from 1 to 22 months (mean±SD 5±3 months). Pathology included diffuse astrocytoma (WHO grade II) in 2 patients, oligodendroglioma (WHO grade II) in 3, oligoastrocytoma (WHO grade II) in 4, and glioblastoma (WHO grade IV) in 5 patients.

### fMRI acquisition

fMRI was performed using a Siemens Medical Systems Trio 3.0 T magnetic resonance (MR) scanner equipped at the Beijing Brain MRI Center. Each subject underwent a localizing image scan followed by a T2 structure image scan; a T2-weighted functional image was scanned at the same location (T2-weighted gradient echo, echo-planner imaging, repetition time (TR)=2000 ms, echo time (TE)=29 ms, flip angle=90°, field of view (FOV)=220×220 $mm^2$, acquisition matrix=64×64, voxel size=3.4×3.4×4.0 $mm^3$); finally, a T1-weighted three-dimensional structure image was acquired (TR=3560 ms, TE=5 ms, flip angle=90°, field of view=256×256 $mm^2$, matrix=256×256, voxel size=1.0×1.0×1.0 $mm^3$).

Informed consent complying with local institutional review board regulations was obtained from all patients. A silent reading task was performed, in which patients were asked to read the Chinese characters presented on the screen silently and to understand the meaning of each word or sentence. The stimuli were a paragraph composed of Chinese characters [11, 12], which were shown through a light-emitting diode (LED) projector system. During the paradigm, a set of 2 trials (30 s each) was performed and interleaved with 3 control conditions (20 s each), in which the patient was instructed to maintain fixation on a crosshair. Prior to fMRI scanning, all patients were trained with the paradigm using stimuli different from those presented during the protocol, and they demonstrated their ability to perform the task.

### fMRI data analysis

fMRI data was processed on a Matlab 8.4 workstation (the MathWorks) using SPM 12 (London University) and xjView toolbox. Maps were generated by identifying every voxel that exceeded a predetermined significance threshold ($P<0.001$) and overlaying these voxels on T1-weighted structure images to display the anatomical location of brain activity.

Language cortex reorganization was studied in the Broca (inferior frontal and middle frontal gyri, including Brodmann area 44, 45, 9, 46) and Wernicke (supramarginal, angular, and superior temporal gyri, including Brodmann area 22, 21, 39, 40) areas [13], using LI to quantify the degree of lateralization of BOLD signal activations. It was calculated for Broca and Wernicke areas separately, and the global LI was also calculated using the following formula: LI=(VL−VR)/(VL+VR), where VL denotes the number of voxels activated in the left hemisphere and VR denotes the number of voxels activated in the right hemisphere. LI ranged from −1 to +1 and language lateralization was categorized into 3 patterns. An LI less than or equal to −0.2 was considered right-sided lateralization, whereas an LI greater than or equal to 0.2 s was regarded as left-sided lateralization, and an LI between −0.2 and 0.2 suggested no clear hemispheric preference [14].

For AVM patients, lesion size, deep drainage veins, and Spetzler-Martin grade were determined from digital subtraction angiography (DSA) and MR images. Lesion size was defined by the maximum diameter of the nidus. fMRI data was used for intraoperative neuronavigation. All patients were surgically treated, and the diagnoses were confirmed by pathology examinations.

### Statistical analysis

All statistical analyses were performed with SPSS (Windows version 18.0, IBM). Independent *t* test, Wilcoxon rank-sum test, and chi-square test were performed to analyze the difference of BOLD signal lateralization between groups. Odds ratio with 95 % confidence interval (CI) was presented. A probability value <0.05 was considered statistically significant.

## Results

### AVM-L group analysis

In the AVM-L group, the mean maximum diameter of lesions was 29.5±7.3 mm (range 10 to 40 mm). According to the Spetzler-Martin grading system, there were 10 grade I patients, 12 grade II patients, 4 grade III patients, and 1 grade IV patients. As shown in Table 1, 6 patients showed right dominance according to the global LI. According to the prior criteria, right-sided BOLD signal lateralization was observed in 10 patients (33.3 %). Three patients had right-sided lateralization in both Broca (LI=−0.50±0.24) and Wernicke (LI=−0.51±0.07) areas (Fig. 1), 6 in the Broca area alone (LI=−0.42±0.22), and 1 in the Wernicke area alone (LI=−0.50) (Table 1).

### AVM-R group analysis

The maximum diameter of lesions ranged from 20 to 40 mm (mean±SD 32.5±8.0 mm). There were 3 grade I patients, 7

**Table 1** Number of patients with right-sided lateralization of BOLD signals in AVM, CM, and Glioma groups

| Groups | Number of patients with right-sided lateralization of BOLD signal activations | | | | |
|---|---|---|---|---|---|
| | Globally[a] | Broca area alone | Wernicke area alone | Both Broca and Wernicke areas | None |
| AVM-L group ($n$=27) | 6 | 6 | 1 | 3 | 17 |
| AVM-R group ($n$=14) | 0 | 0 | 0 | 0 | 14 |
| CM-L group ($n$=29) | 3 | 0 | 0 | 3 | 26 |
| CM-R group ($n$=20) | 0 | 0 | 0 | 0 | 20 |
| Glioma-L group ($n$=20) | 0 | 0 | 1 | 0 | 19 |
| Glioma-L group ($n$=14) | 0 | 0 | 0 | 0 | 14 |

[a] Right-sided lateralization of BOLD signal activations according to the global LI

grade II patients, 3 grade III patients, and 1 grade IV patients. No patient had right-sided lateralization (Table 1).

### Difference between AVM-L group and AVM-R group

Between the AVM-L group and AVM-R group, there was no significant difference in gender ($P$=0.228, by chi-square test), age ($P$=0.926, by independent $t$ test), lesion size ($P$=0.233, by independent $t$ test), incidence of deep drainage vein ($P$=0.548, by chi-square test), or Spetzler-Martin grade ($P$=0.280, by Wilcoxon rank-sum test). However, right-sided lateralization of BOLD signals was significantly more common in the AVM-L group (37.0 %) than in AVM-R group (0.0 %) ($P$=0.025, by chi-square test). Regarding clinical symptoms, although 1 patient in the AVM-L group presented with aphasia and no patient in the AVM-R group had aphasia, no significant difference was observed between them ($P$=1.000, by Fisher's exact test).

### CM-L group analysis

The mean maximum diameter of lesions was 15.4±6.1 mm (range 5 to 30 mm). As shown in Table 1, 3 patients had right-sided BOLD signal lateralization according to the global LI, and these 3 patients (10.3 %) also showed right-sided lateralization of both the Broca (LI=−0.41±0.14) and Wernicke (LI=−0.75±0.23) areas (Fig. 2). The other patients were all left-sided lateralized.

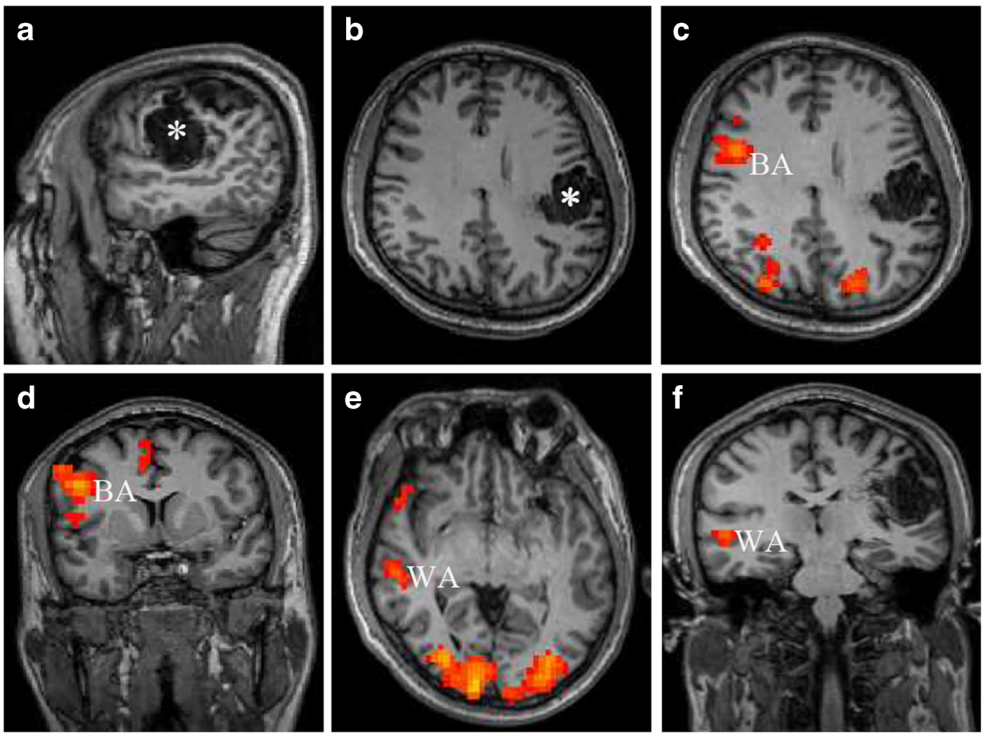


**Fig. 1** MR images of a patient in the AVM-L group. T1-weighted sagittal (**a**) and axial (**b**) MR images revealed an AVM (*asterisk*) involving Broca area. Axial and coronal fMR images showed right-sided BOLD signal activation of both Broca (**c**, **d** *BA*) and Wernicke (**e**, **f** *WA*) areas

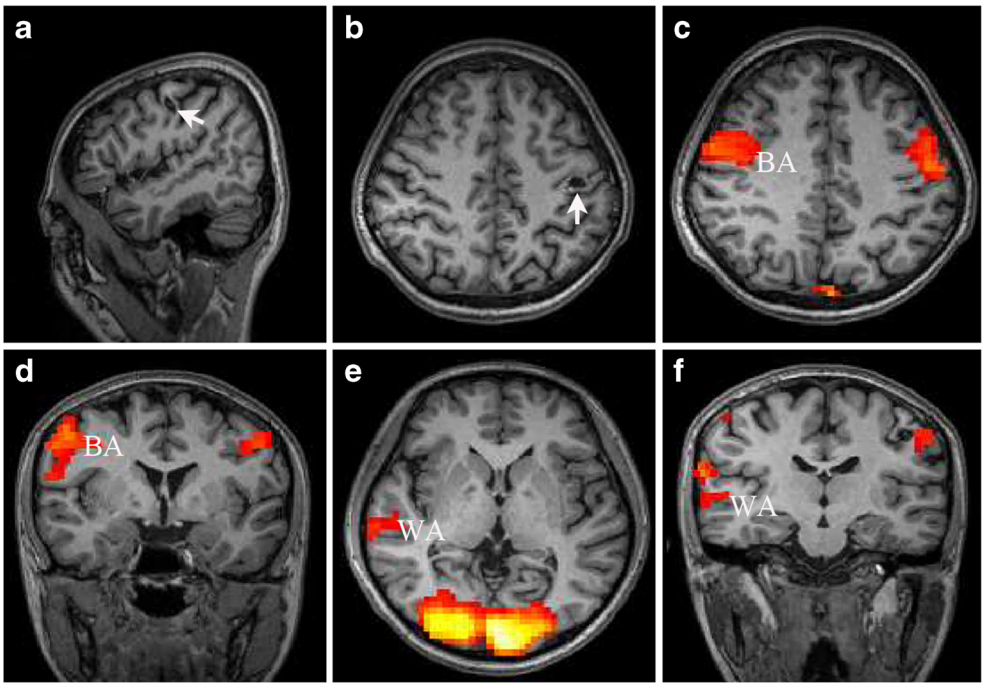


**Fig. 2** MR images of a patient in CM-L group. T1-weighted sagittal (**a**) and axial (**b**) MR images revealed a small CM (*white arrow*) adjacent to the Broca area. Axial (**c**) and coronal (**d**) fMR images showed bilateral activation of the Broca area (*BA*), which was categorized into right-sided lateralization according to the criteria. Axial (**e**) and coronal (**f**) fMR images demonstrated right-sided lateralization of the Wernicke area ("WA")

### CM-R group analysis

The maximum diameter of lesions ranged from 5 to 25 mm (mean±SD 15.0±5.6 mm). As shown in Table 1, no patient had right-sided BOLD signal lateralization. Only 1 patient showed no clear hemispheric preference of both Broca (LI=−0.06) and Wernicke areas (LI=−0.05).

### Difference between CM-L group and CM-R group

Between the CM-L group and CM-R group, there was no significant difference in gender ($P$=0.644, by chi-square test), age ($P$=0.979, by independent $t$ test), or lesion size ($P$=0.787, by independent $t$ test). Although the incidence of right-sided lateralization of BOLD signals was higher in the CM-L group (10.3 %) than in CM-R group (0 %), no significant difference was observed ($P$=0.380, by chi-square test). Likewise, although 3 patients in the CM-L group presented with aphasia and no patient in the CM-R group had aphasia, there was also no significant difference ($P$=0.380, by chi-square test).

### Glioma-L group analysis

The maximum diameter of lesions ranged from 24 to 40 mm (mean±SD 31.7±5.5 mm). No patient had right-sided lateralization according to the global LI (Table 1). Only 1 patient (5.0 %) showed no clear hemispheric preference of the Broca area (LI=0.02) and right-sided BOLD lateralization of the Wernicke area (LI=−0.40) (Fig. 3). The other patients were all left-sided lateralized.

### Glioma-R group analysis

The maximum diameter of lesions ranged from 22 to 40 mm (mean±SD 31.4±6.1 mm). As shown in Table 1, no patient had right-sided lateralization according to the global LI. Only 1 patient showed no clear hemispheric preference of the Wernicke area (LI=−0.04). The other patients were all left-sided lateralized.

### Difference between Glioma-L group and Glioma-R group

Between the Glioma-L group and Glioma-R group, there was no significant difference in gender ($P$=1.000, by Fisher's exact test), age ($P$=0.769, by independent $t$ test), or lesion size ($P$=0.913, by independent $t$ test). The incidence of aphasia was significantly higher in the Glioma-L group (45.0 %) than that in the Glioma-R group (0 %) ($P$=0.004, by chi-square test). Although the incidence of right-sided lateralization of BOLD signals was higher in the Glioma-L group (5.0 %) than in the Glioma-R group (0 %), no significant difference was observed ($P$=1.000, by Fisher's exact test).

### Difference between AVM-L group and CM-L group

As regards the AVM-L group and CM-L group, there was no significant difference in gender ($P$=0.774, by chi-square test) or age ($P$=0.197, by independent $t$ test). The lesions were significantly larger in the AVM-L group than in the CM-L group ($P$<0.001, by independent $t$ test). And the incidence of right-sided lateralization of BOLD signal activations was significantly higher in the AVM-L group (37.0 %) than in the CM-L group

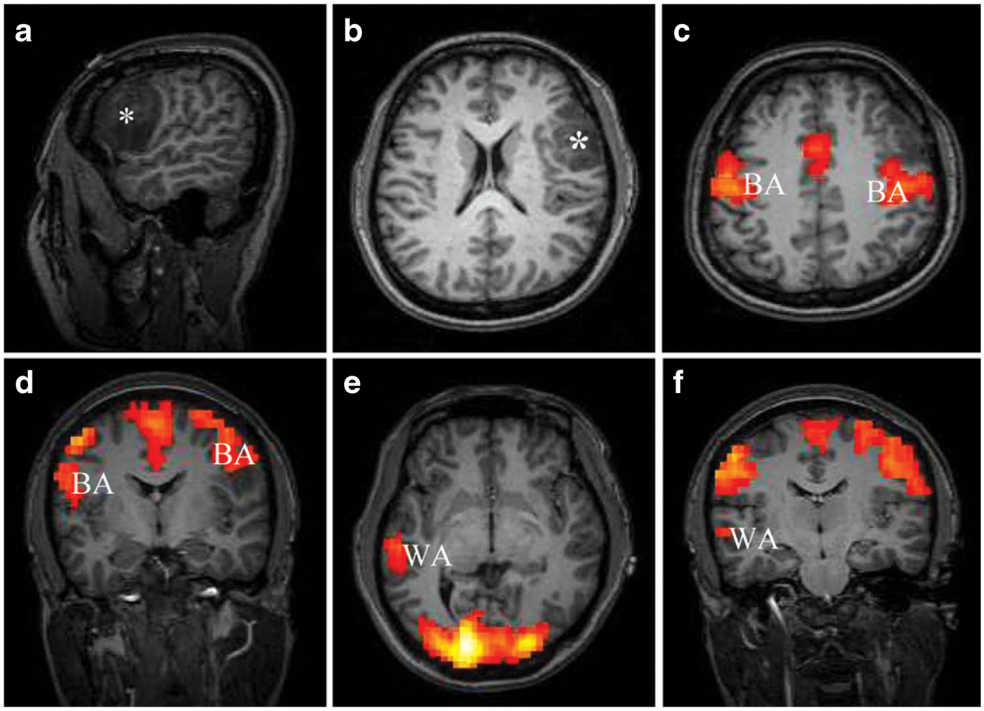


**Fig. 3** MR images of a patient in the Glioma-L group. T1-weighted sagittal (**a**) and axial (**b**) MR images revealed a glioma (*asterisk*) adjacent to the Broca area. Axial (**c**) and coronal (**d**) fMR images showed bilateral activation of the Broca area (*BA*), which was categorized into no clear hemispheric preference. Axial (**e**) and coronal (**f**) fMR images demonstrated right-sided lateralization of the Wernicke area (*WA*)

(10.3 %) ($\chi^2$ 5.589, $P$=0.018, OR=5.089, 95 % CI 1.223, 21.254). Besides, although the incidence of aphasia is higher in the CM-L group (10.3 %) than in the AVM-L group (3.7 %), there was no significant difference ($P$=0.656, by chi-square test).

### Difference between AVM-L group and glioma-L group

Regarding the AVM-L group and Glioma-L group, there was no significant difference in gender ($P$=0.474, by chi-square test) or lesion size ($P$=0.273, by independent $t$ test). Patients of the Glioma-L group was significantly older than those of the AVM-L group ($P$=0.001, by independent $t$ test). The incidence of aphasia is significantly higher in the Glioma-L group (45.0 %) than in the AVM-L group (3.7 %) ($P$=0.002, by chi-square test). And right-sided lateralization of BOLD signal activations was significantly more common in the AVM-L group (37.0 %) than in the Glioma-L group (5.0 %) ($\chi^2$ 4.912, $P$=0.027, OR=11.176, 95 % CI 1.292, 96.647).

### Difference between CM-L group and glioma-L group

There was no significant difference in gender ($P$=0.644, by chi-square test). Patients of the Glioma-L group was significantly older than those of the CM-L group ($P$=0.013, by independent $t$ test), and the lesion size was significantly smaller in the CM-L group than in the Glioma-L group ($P$<0.001, by independent $t$ test). Besides, the incidence of aphasia is significantly higher in the Glioma-L group (45.0 %) than in the CM-L group (10.3 %) ($\chi^2$ 5.928, $P$=0.015, OR=7.091, 95 % CI 1.607, 31.292). And there was no significant difference in the incidence of right-sided lateralization of BOLD signal activations ($P$=0.888, by chi-square test).

## Discussion

Previous studies have demonstrated language reorganization in the setting of various pathological entities, including AVMs [5, 15–17], strokes [18], epilepsies [19], brain tumors [8, 9, 20, 21], etc. The language reorganization in AVM patients has been particularly the concern, and it has been noticed that unruptured AVMs located in language cortex usually do not lead to aphasia. However, few studies have focused on the language reorganization in CM patients, which might be underestimated [6]. It was speculated that CM lesions might be too small to induce language reorganization [3]. In contrast, gliomas are thought to be acquired diseases and aphasia is a common presentation for patients with gliomas involving language areas. So far, little is known about the difference of language cortex reorganization between AVMs, CMs, and gliomas. Besides, most of the prior reports have focused on global LI as a measure of language lateralization, and activations of Broca and Wernicke areas were seldom separately discussed. However, it is reported that Broca and Wernicke areas can be asymmetrically lateralized in the setting of intracranial lesions [13, 14, 17]. In this case, studying the global LI alone might be inappropriate, which could lead to wrong conclusions of language lateralization, because the activated voxels in different hemispheres will offset each other according to the formula of LI.

Therefore, we conducted this study to compare the ability of language cortex reorganization between AVMs, CMs, and gliomas, with activations of the Broca and Wernicke areas separately analyzed. Due to lack of CM patients with lesions involving the Wernicke area, we only evaluated the AVM, CM, and glioma patients with lesions located in the Broca area in this study.

### Modalities for language mapping

Clinically, there are several techniques for language mapping, including fMRI, magnetoencephalography (MEG), radionuclide scanning (SPECT and PET), Wada testing, and electrocortical stimulation mapping (ESM). Wada testing has long been considered the gold standard for preoperative assessment of language dominance, but it is invasive and does not provide the topographic specificity as offered by fMRI. ESM has conventionally been accepted as the gold standard for intraoperative localization of the lingual areas. However, this technique might be risky due to conscious anesthesia, extension of operation time, the inability of some patients to cooperate, and potential induction of epilepsy [22]. Moreover, in patients with cortical functional areas that have been reorganized in the contralateral hemisphere, ESM would not be feasible as it would require a craniotomy on the contralateral side [23].

Meanwhile, fMRI has emerged as the leading noninvasive modality for preoperative language mapping. Some authors have questioned the accuracy of fMRI, especially in AVM patients [24]. They hypothesized that AVMs could lead to reduction of cerebral perfusion around extranodal tissues (arterial steal), resulting in abnormal fMRI results, as BOLD fMRI is dependent on blood oxygen levels [24]. Nevertheless, most studies focusing on comparison of fMRI and ESM have demonstrated that fMRI is actually a very sensitive imaging modality, even in patients with vascular malformations [25, 26].

In this study, considering bilateral activation is common in fMRI images, patients with lesions involving right inferior frontal lobe (homologous regions of the Broca area) were also enrolled to evaluate if right-sided lateralization could also be observed in these patients. Results showed right-sided lateralization occurred in 10 of the 27 patients in the AVM-L group and no patient in the AVM-R group. Although there was no significant difference between the AVM-L group and AVM-R group in gender, age, lesion size, incidence of deep drainage veins, or Spetzler-Martin grade, right-sided lateralization was significantly more common in the AVM-L group (10.3 %) than in the AVM-R group (0 %) ($P$=0.025). Likewise, right-sided lateralization was detected in 3 of the 29 patients in the CM-L group and no patient in the CM-R group. Although there was no significant difference, the incidence of right-sided lateralization was higher in the CM-L group (10.3 %) than in the CM-R group (0 %). Also, right-sided lateralization of BOLD signals was observed in 1 patient in the Glioma-L group and no patient in the Glioma-R group. All these results supported that the right-sided lateralization on fMRI was true rather than a lesion-induced pseudo right dominance.

### Comparison between AVM-L group and CM-L group

Language reorganization in AVM patients has been reported, but little is known in CM patients. We can only find one case of CM with right-sided lateralization in the literature, which only showed shifting of the Wernicke area [6]. In our study, we detected 3 CM patients with right-sided lateralization of both the Broca and Wernicke areas. As shown in Fig. 2, even very small CMs can lead to language reorganization.

In this study, right-sided lateralization of BOLD signal activations was observed in both the AVM-L group and CM-L group, suggesting that language cortex reorganization may occur in both AVMs and CMs when they involve language areas. However, compared with the CM-L group, the incidence of right-sided lateralization was significantly higher in the AVM-L group ($P$=0.018), which suggested AVM patients had a greater need of language cortex reorganization than CM patients.

Both AVMs and CMs are generally considered as congenital vascular lesions. Although the exact period in which cerebral AVMs and CMs occur is still controversial, there is a consensus that they develop in early life [16, 27]. And it is reported that the brain possesses a greater ability of plasticity in its immature than in its mature state [8]. Consequently, when AVMs and CMs develop in the anatomical site of eloquent cortex in early life, neuroplasticity may result in cortical reorganization of the functional areas, with displacement to homologous regions on the contralateral side or to the cortex around the lesion on the same hemisphere. Language function will therefore seldom be impaired [5]. This explains why right-sided lateralization of BOLD signal activations occurs in both the AVM-L group and CM-L group.

Meanwhile, as regards the difference of language cortex reorganization between AVM and CM patients, we speculate it may result from the following reasons. First, lesion size might be an important factor affecting right dominance. In our study, the volume of CMs is significantly smaller than that of AVMs. It is speculated that when CMs develop in language areas, they might be too small to impair language functions, and reorganization therefore seldom appears. Meanwhile, nidus of AVMs might be big enough to impair language function; thus, the language cortex has to be reorganized to the contralateral side or to the cortex surrounding the lesion on the same hemisphere. Therefore, we believe that compared to AVM patients, there is little need of language cortex reorganization for CM patients. However, apparently, lesion size is not the only reason because we found lesion size did not significantly affect right-sided lateralization in both the AVM-L group and CM-L group. Even very small nidus may lead to language reorganization and large lesions may not.

Histopathological differences between AVMs and CMs may be another factor leading to the difference. AVMs are characterized by massive abnormal vessels, and there is usually brain parenchyma within the nidus, although these tissues might be nonfunctional. On the contrary, CMs are composed of thin hyalinized vascular channels without interposed brain tissue. In addition, compared with AVMs, CMs have a lower flow rate; therefore, CMs are less disruptive of the hemodynamics of the adjacent brain tissues. We think all the above factors may work together and induce the difference in language cortex reorganization between cerebral AVMs and CMs.

### Comparison between AVM-L group and glioma-L group

In this study, although there was no significant difference in gender or lesion size, the incidence of right-hemisphere lateralization was significantly higher in the AVM-L group (37.0 %) than in the Glioma-L group (5.0 %) ($P$=0.027). And language dysfunction is more common in the Glioma-L group (45.0 %) than in the AVM-L group (3.7 %) ($P$=0.002). Unlike CMs, we believe the lesions of both AVMs and gliomas should be big enough to impair language function; thus, language reorganization is needed in both AVMs and gliomas. Therefore, we think the above results suggested that AVM patients have a greater capacity of language cortex reorganization than glioma patients.

We speculate this difference may result from several reasons. First, the stage of lesion development might be a factor affecting the potential of language reorganization. AVMs are thought to be congenital disease and develop in early life [16, 27], but gliomas are acquired diseases which mainly develop in adult patients. So, we believe the probable reason is that the brain possesses a greater ability of plasticity in its immature than in its mature stage. Second, duration of illness might be another reason. Unruptured AVMs are chronic diseases with a long duration of illness, whereas the course of tumors is relatively short. So, we speculate the brain has a greater ability of reorganization in the setting of a chronic disease rather than an acute disease. Moreover, the histopathological differences may play a role. AVMs are characterized by massive malformed vessels, and mass effect seldom occurs unless AVMs ruptured. On the contrary, gliomas do not have the abnormal vessels like AVMs, and mass effect usually exists. We think all the above factors may result in the difference in language cortex reorganization between AVMs and gliomas.

### Limitations of the study

The present study has several limitations. First, this is an fMRI study, and the confirmatory tests (ESM and Wada testing) were not conducted, which would be useful to confirm the results. Second, since we do not know the exact language cortex location without ESM, the relationship between right-sided dominance and the distance between the lesion and the language area was not studied in this manuscript. Third, only a silent reading task was performed in this study. Although activations of both Broca and Wernicke areas were observed in all patients, multiple tasks may make our conclusions more reliable. Fourth, this study only enrolled patients with lesions involving the Broca area, and those involving the Wernicke area were not studied. Moreover, even if both AVMs and CMs are considered to be congenital diseases, they are not necessarily present during cerebral maturation. And the lesion size during the stage of language acquisition is very important to study language cortex reorganization. However, these data are unavailable. Therefore, we have to study the lesions in adult patients. Overall, further studies with a large series of patients undergoing both multiple-task fMRI and confirmatory tests are needed to confirm our conclusions.

## Conclusions

Language cortex reorganization may occur in cerebral AVMs, CMs, and gliomas when lesions involve language cortex. However, the potential of reorganization for CM and glioma patients seems to be insufficient compared with AVM patients. For the difference of AVMs and CMs, the possible reason is that CMs have little “need” for language reorganization. Meanwhile, for AVMs and gliomas, the difference should be regarded as AVMs have a greater capacity for language reorganization because language reorganization is needed in both AVMs and gliomas. More specifically, we speculate the difference might be attributed to the histopathological difference, development stage, duration of illness, lesion size, and hemodynamic effects. Lesion size is not the only reason leading to this difference, and even very small nidus can induce right-sided lateralization.

**Acknowledgments** This study is granted by the Ministry of Science and Technology of China grant (2012CB825505 and 2011BAI08B08), National Key Technology Research and Development Program of the Ministry of Science and Technology of China (2013BAI09B03), and Center of Stroke, Beijing Institute for Brain Disorders (BIBD-PXM2013_014226_07_000084).

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no competing interests.

## References

1. Choi JH, Mohr JP (2005) Brain arteriovenous malformations in adults. Lancet Neurol 4:299–308

2. Mohr JP (2005) Brain arteriovenous malformations: children and adults. Stroke 36:2060–2061
3. Jeon JS, Kim JE, Chung YS, Oh S, Ahn JH, Cho WS, Son YJ, Bang JS, Kang HS, Sohn CH, Oh CW (2014) A risk factor analysis of prospective symptomatic haemorrhage in adult patients with cerebral cavernous malformation. J Neurol Neurosurg Psychiatry 85: 1366–1370
4. Moultrie F, Horne MA, Josephson CB, Hall JM, Counsell CE, Bhattacharya JJ, Papanastassiou V, Sellar RJ, Warlow CP, Murray GD, Al-Shahi SR (2014) Outcome after surgical or conservative management of cerebral cavernous malformations. Neurology 83: 582–589
5. Alkadhi H, Kollias SS, Crelier GR, Golay X, Hepp-Reymond MC, Valavanis A (2000) Plasticity of the human motor cortex in patients with arteriovenous malformations: a functional MR imaging study. AJNR Am J Neuroradiol 21:1423–1433
6. Maestu F, Saldana C, Amo C, Gonzalez-Hidalgo M, Fernandez A, Fernandez S, Mata P, Papanicolaou A, Ortiz T (2004) Can small lesions induce language reorganization as large lesions do? Brain Lang 89:433–438
7. Dronkers NF, Wilkins DP, Van Valin RD Jr, Redfern BB, Jaeger JJ (2004) Lesion analysis of the brain areas involved in language comprehension. Cognition 92:145–177
8. Duffau H (2013) The huge plastic potential of adult brain and the role of connectomics: new insights provided by serial mappings in glioma surgery. Cortex 58:325–337
9. Rosler J, Niraula B, Strack V, Zdunczyk A, Schilt S, Savolainen P, Lioumis P, Makela J, Vajkoczy P, Frey D, Picht T (2013) Language mapping in healthy volunteers and brain tumor patients with a novel navigated TMS system: evidence of tumor-induced plasticity. Clin Neurophysiol 125:526–536
10. Fuller GN, Scheithauer BW (2007) The 2007 revised world health organization (WHO) classification of tumours of the central nervous system: newly codified entities. Brain Pathol 17:304–307
11. Tan LH, Feng CM, Fox PT, Gao JH (2001) An fMRI study with written Chinese. Neuroreport 12:83–88
12. Tan LH, Liu HL, Perfetti CA, Spinks JA, Fox PT, Gao JH (2001) The neural system underlying Chinese logograph reading. Neuroimage 13:836–846
13. Rutten GJ, Ramsey NF, van Rijen PC, Alpherts WC, van Veelen CW (2002) FMRI-determined language lateralization in patients with unilateral or mixed language dominance according to the Wada test. Neuroimage 17:447–460
14. Lee DJ, Pouratian N, Bookheimer SY, Martin NA (2010) Factors predicting language lateralization in patients with perisylvian vascular malformations. Clin Article J Neurosurg 113:723–730
15. La Piana R, Klein D, Cortes M, Tampieri D (2009) Speech reorganization after an AVM bleed cured by embolization. A case report and review of the literature. Interv Neuroradiol 15:456–461
16. Lehericy S, Biondi A, Sourour N, Vlaicu M, Du MST, Cohen L, Vivas E, Capelle L, Faillot T, Casasco A, Le BD, Marsault C (2002) Arteriovenous brain malformations: is functional MR imaging reliable for studying language reorganization in patients? Initial observations. Radiology 223:672–682
17. Vikingstad EM, Cao Y, Thomas AJ, Johnson AF, Malik GM, Welch KM (2000) Language hemispheric dominance in patients with congenital lesions of eloquent brain. Neurosurgery 47:562–570
18. Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF, Heiss WD (2005) Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: a combined repetitive transcranial magnetic stimulation and positron emission tomography study. Stroke 36:1759–1763
19. Janszky J, Mertens M, Janszky I, Ebner A, Woermann FG (2006) Left-sided interictal epileptic activity induces shift of language lateralization in temporal lobe epilepsy: an fMRI study. Epilepsia 47: 921–927
20. Sanai N, Mirzadeh Z, Berger MS (2008) Functional outcome after language mapping for glioma resection. N Engl J Med 358:18–27
21. Wang L, Chen D, Yang X, Olson JJ, Gopinath K, Fan T, Mao H (2013) Group independent component analysis and functional MRI examination of changes in language areas associated with brain tumors at different locations. PLoS One 8, e59657
22. Ojemann G, Ojemann J, Lettich E, Berger M (2008) Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg 108: 411–421
23. Lee L, Sitoh YY, Ng I, Ng WH (2013) Cortical reorganization of motor functional areas in cerebral arteriovenous malformations. J Clin Neurosci 20:649–653
24. Ulmer JL, Hacein-Bey L, Mathews VP, Mueller WM, DeYoe EA, Prost RW, Meyer GA, Krouwer HG, Schmainda KM (2004) Lesion-induced pseudo-dominance at functional magnetic resonance imaging: implications for preoperative assessments. Neurosurgery 55:569–579
25. Cannestra AF, Pouratian N, Forage J, Bookheimer SY, Martin NA, Toga AW (2004) Functional magnetic resonance imaging and optical imaging for dominant-hemisphere perisylvian arteriovenous malformations. Neurosurgery 55:804–812
26. Pouratian N, Bookheimer SY, Rex DE, Martin NA, Toga AW (2002) Utility of preoperative functional magnetic resonance imaging for identifying language cortices in patients with vascular malformations. J Neurosurg 97:21–32
27. Gross BA, Du R (2013) Natural history of cerebral arteriovenous malformations: a meta-analysis. J Neurosurg 118:437–443


## Comments

Peter Willems, Leiden, The Netherlands

The authors describe an interesting retrospective fMRI analysis of surgical cases harboring an arteriovenous malformation (AVM), a cavernous malformation (CM), or a glioma in or near the Broca area (assumed to reside in the left hemisphere) or its homology in the contralateral hemisphere. They conclude that AVMs more frequently cause language area reorganization than CMs or gliomas, while they produce aphasia less frequently. One would expect functional cerebral reorganization to occur when two conditions are met: the brain tissue responsible for a specific function should be sufficiently disturbed and sufficient neuroplasticity should be present to allow that function to relocate. The first condition is likely influenced by lesion size and should definitely be regarded as fulfilled if functional impairment occurs (in this case aphasia). The second condition is likely influenced by patient age at the time of lesion growth and by the lesion growth rate. Thus, if a lesion develops early and slowly, no aphasia should occur due to relocation of function. This is in close agreement with the findings for AVMs. On the other hand, if a lesion develops late and fast, aphasia may occur but will not lead to relocation of function, as the results show for gliomas. The CM results are more difficult to categorize. There were some cases with aphasia, but also some cases with relocation of language function. Perhaps some of these lesions may lead to reorganization because they do disturb the language area at a sufficiently young age, while others just remain too small or take too long to reach the size that will induce aphasia.